AMERICAN JOURNAL OF EPIDEMIOLOGY
Vol. 129, No. 3
Printed in U.S.A.

MAMMOGRAPHIC PARENCHYMAL PATTERNS AS INDICATORS OF BREAST CANCER RISK

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Saftlas, A. F. (CDC, Atlanta, GA 30333), J. N. Wolfe, R. N. Hoover, L. A. Brinton, C. Schairer, M. Salane, and M. Szklo. Mammographic parenchymal patterns as indicators of breast cancer risk. *Am J Epidemiol* 1989;129:518–26.

Mammographic parenchymal patterns have been suggested as indicators of breast cancer risk. However, few well-controlled studies have used prediagnostic mammograms to determine the pattern classification. The authors studied 266 cases of breast cancer and 301 controls from 25 screening centers of the Breast Cancer Detection and Demonstration Project, a nationwide screening program conducted between 1973 and 1980 to evaluate the risk associated with mammographic patterns using mammograms taken four years before the detection of breast cancer. Mammograms of the cancerous breast of cases and of the ipsilateral breast in the control matched to each case were blindly assessed by one of the investigators (J. N. W.), originator of the mammographic pattern classification. The breast cancer odds ratio among women with the combined P2 + DY patterns, compared with women with the N1 pattern, was 2.8 (95% confidence interval (CI): 1.6–5.1). This estimate of relative risk was comparable with the risk associated with other recognized breast cancer risk factors. The odds ratio among P2 + DY women with a first-degree family history of breast cancer was 5.5 (95% CI: 2.6–11.8) compared with N1 women without a family history. These data provide additional evidence that mammographic patterns are indicators for subsequent development of breast cancer, particularly among women with a first-degree family history of this malignancy.

breast neoplasms; hereditary diseases; mammography

In 1976, Wolfe first proposed mammographic parenchymal patterns as indicators for predicting the risk of breast cancer (1, 2), postulating that four patterns—N1, P1, P2, and DY—were associated with a stepwise increase in breast cancer risk.

In Wolfe's initial studies (1, 2), high risks of breast cancer were associated with the

Received for publication November 30, 1987, and in final form June 17, 1988.

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Supported in part by Institutional Research Cancer Epidemiology Fellowship T 32 CA09314-07 from the National Cancer Institute.

The authors thank Linda Lannom of WESTAT, Inc., for supervising the data collection, Dr. Ann Dudgeon of ORI, Inc., for programming assistance, and Dr. Carol A. Newill for helpful suggestions. The authors also acknowledge the invaluable assistance of the directors and coordinators of the Breast Cancer Detection and Demonstration Project centers who provided the study mammograms.

P2 and DY patterns. Subsequent studies by numerous investigators (3–21), however, have differed widely in their conclusions. Methodological differences are likely to be responsible for the broad range of reported findings (22, 23). For example, most studies (22, 23) did not adjust for potentially confounding breast cancer risk factors or assess the agreement of their classifications with those of Wolfe. Moreover, some studies (3–6, 12, 13, 16) conducted unblinded pattern assessments or revised the definitions of the parenchymal pattern categories, making it difficult to compare findings of different studies. Although reviews of the literature on the parenchymal pattern suggest that most methodologically sound studies have reported positive associations of Wolfe's classification with breast cancer risk, the relation of mammographic patterns with breast cancer remains controversial.

To address this issue, we conducted a case-control study of screening program participants to examine the breast cancer risk associated with mammographic parenchymal patterns on mammograms taken four years before the diagnosis of breast cancer.

Materials and Methods

Wolfe's mammographic classification is based solely on the radiographic appearance of the breast parenchyma (1, 2). N1, the breast pattern that has been associated with the lowest risk of breast cancer, is composed primarily of fat with few minor and scattered densities (24). The P1 breast is also fatty, but contains prominent ducts occupying less than 25 per cent of the breast area. The P2 breast contains prominent ductal densities (linear and nodular densities) that occupy 25–100 per cent of the breast area; it differs from the P1 breast only with respect to the area of the breast containing prominent ductal densities. The DY pattern is characterized by irregular sheetlike regions of homogenous densities and shows no sign of the prominent ductal pattern. If homogenous densities appear in the presence of ductal densities, a P1 or P2 classification is assigned (24).

The study population consisted of women who participated in the Breast Cancer Detection and Demonstration Project, a nationwide screening program sponsored jointly by the National Cancer Institute and the American Cancer Society. Between 1973 and 1975, this program recruited more than 280,000 women to receive five annual screening evaluations that included a clinical examination, mammography, and thermography.

Case subjects ($n = 266$) from 25 of the 29 Breast Cancer Detection and Demonstration Project screening centers were diagnosed with unilateral breast cancer during the fifth year of the Project, and had no prior history of the disease. Most subjects with breast cancer were diagnosed from 1978 to 1980. The controls ($n = 301$) were from the same screening centers as the cases but did not receive a recommendation for biopsy during the program. They were matched to the cases on screening center, age at entry (within five-year age groups), race (white, black, Oriental, and other), time of entry into the Project (within six months), and length of continuation in the Project (to ensure an equal opportunity for diagnosis).

All case and control subjects were interviewed in their homes by trained interviewers during the course of a large case-control study described in detail elsewhere (25). Interviews lasted approximately one hour and included questions relating to family history of breast cancer, reproductive and menstrual history, use of exogenous hormones, medical history, body build, drinking and smoking habits, and sociodemographic information. Interviews were completed for 85.4 per cent of the cases eligible for this study and 90.4 per cent of their matched controls. Reasons for interviews not obtained included death (2.9 per cent of the cases vs. 0.9 per cent of the controls), illness (2.3 per cent of the cases vs. 0.6 per cent of the controls), relocation (2.0 per cent of the cases vs. 1.4 per cent of the

controls), and refusal (7.1 per cent of the cases vs. 6.2 per cent of the controls).

All study mammograms were taken during the first screening year of the Project and classified according to mammographic pattern by Dr. Wolfe. Approximately 72 per cent of the study mammograms were produced by xeromammography, whereas 28 per cent were film screen mammograms. Among cases, the breast subsequently found to have cancer was analyzed by parenchymal pattern, whereas the pattern of the ipsilateral breast was evaluated in matched controls. Dr. Wolfe assessed the caudal and lateral views of each breast simultaneously, assigning one pattern classification to each pair of mammograms (i.e., pair = caudal and lateral view). All mammograms were classified without knowledge of case-control status, patient's age, examination date, or screening center.

Odds ratios (OR) were calculated to assess the magnitude of the relation of breast cancer to mammographic parenchymal patterns, using the N1 pattern as the referent category. Although a matched study design was used, unmatched logistic regression findings are presented because similar results were obtained using a matched analysis (26, 27), and the unmatched analyses provided more stable estimates of risk by retaining greater numbers of cases and controls. Logistic regression was used to identify and adjust for the effects of one or more confounding variables (28). Variables examined for confounding included weight at entry, height at entry, family history of breast cancer, age at first livebirth, number of livebirths, and number of previous breast biopsies prior to entering the Project. The final logistic model was determined by removing each potentially confounding variable one at a time from the full model. The decision to keep a variable in the model was based on comparisons of adjusted and unadjusted odds ratios associated with the P2 + DY category (referent = N1). Because age at entry was a matching factor, this variable was retained in the model.

The 95 per cent confidence intervals were calculated by the method of Gart (29). Tests for trend in odds ratios associated with mammographic parenchymal patterns were obtained by scoring this categorical variable with an ordered code (e.g., 1, 2, 3) and treating it as a continuous variable. We combined the P2 and DY parenchymal patterns for subgroup analyses because of small numbers of DY women and the similarity of the odds ratios associated with these patterns within the various population subgroups.

Variables suspected of modifying the effect of mammographic patterns on breast cancer risk were evaluated assuming null hypotheses for interaction under the multiplicative and additive models (30, 31). The values corresponding to interaction terms in the logistic regression model were used to determine the statistical significance of interactions under the multiplicative model (30, 31). The test for synergy described by Schlesselman (31) was used to assess the statistical significance of interactions under the additive model.

To determine intraobserver reliability, a 10 per cent stratified systematic sample of the study mammograms was drawn and blindly reread by one of the authors (J. N. W.). Reliability data were cross-tabulated according to the parenchymal pattern classifications assigned at the first reading versus those assigned at the second reading. We calculated the per cent agreement between the first and second readings to assess the extent of intraobserver agreement (32).

Results

Evaluation of the frequency distributions of study subjects by age, race, and years of education showed that cases and controls were comparable on these factors. The median ages of cases and controls were 58.0 years and 57.2 years, respectively. White women made up approximately 90 per cent of the cases and controls, whereas blacks and women of other races accounted for the remaining 10 per cent. With respect to education, approximately 50 per cent of cases

and 48 per cent of controls had attended at least one year of college.

Table 1 shows the distribution of cases and controls by parenchymal pattern with the corresponding breast cancer odds ratios. Variables retained in the final regression model included mammographic pattern, age at entry, and weight at entry. Although adjustment for the effects of weight did not influence the odds ratios associated with the P1 pattern, odds ratios associated with the P2 and DY patterns were increased because lighter women were more likely to have the P2 or DY patterns. The odds ratios estimated from the final model were 1.0, 1.5, 2.8, and 2.6 for the N1, P1, P2, and DY patterns, respectively. In addition, there was a significant trend ($p = 0.0001$) in odds ratios associated with the N1, P1, and combined P2 + DY categories. For subsequent analyses, we combined the P2 and DY patterns to compensate for small numbers of DY women in various population subgroups.

Table 2 shows odds ratio estimates associated with recognized risk factors for breast cancer. Odds ratios for each risk factor were simultaneously adjusted for age at entry, parenchymal pattern, and the other risk factors in table 2. Elevated odds ratios were associated with a first-degree family history of breast cancer, having a first livebirth at age 30 years or older, high body weight, and having had two or more breast biopsies prior to entering the screening program. These findings are similar to those observed in other epidemiologic studies of breast cancer (33). Moreover, these data suggest that the relative odds of breast cancer associated with the P2 + DY patterns (OR = 2.8) is comparable with odds ratio estimates associated with recognized breast cancer risk factors in this population.

As a screen for interaction, breast cancer odds ratios associated with Dr. Wolfe's classification were examined within subgroups of the study population. Data in table 3 suggest that the relative risk of breast cancer associated with the P1 and combined P2 + DY parenchymal pattern categories is enhanced among women with a first-degree family history of breast cancer. Note that women in the combined P2 + DY category with a first-degree family history of breast cancer had a risk of breast cancer that was more than five times higher than that among women in the N1 category who had no family history of the disease (OR = 5.5; expected OR under multiplicative model = 2.0; expected OR under additive model = 2.1). A significantly elevated odds ratio of a lower magnitude was associated with the P2 + DY category among women without a family history of breast cancer (OR = 2.2). In contrast, women in the N1 category with a positive family history of the disease had no increased risk of

TABLE 1

*Adjusted breast cancer odds ratios associated with mammographic parenchymal patterns, Breast Cancer Detection and Demonstration Project, 1973–1980**

	Controls ($n = 283$)		Cases ($n = 251$)		Age-adjusted odds ratio†	Age- and weight-adjusted odds ratio‡	95% confidence interval
	n	%	*n*	%			
N1	48	17.0	24	9.6	1.0	1.0	Referent
P1	88	31.1	64	25.5	1.5	1.5	0.8–2.7
P2	111	39.2	129	51.4	2.5	2.8	1.6–5.1
DY	36	12.7	34	13.5	2.2	2.6	1.3–5.4
P2 + DY	147	51.9	163	64.9	2.4	2.8	1.6–5.1

* Unknowns excluded from analysis.

† Adjusted for age at entry (continuous variable).

‡ Adjusted for age at entry (continuous variable) and weight at entry (<55, 55–59, 60–64, 65–74, and ≥75 kg).

TABLE 2

*Odds ratios associated with recognized breast cancer risk factors, Breast Cancer Detection and Demonstration Project, 1973–1980**

Risk factor	No. of cases	No. of controls	Odds ratio†	95% confidence interval
First-degree family history of breast cancer				
No	178	243	1.0	Referent
Yes	73	40	2.3	1.5–3.7
Age at first livebirth (years)				
<20	23	35	1.0	Referent
20–24	76	92	1.2	0.7–2.4
25–29	58	77	1.1	0.5–2.1
≥30	49	40	2.0	1.0–4.2
Nulliparous	45	39	1.5	0.7–3.1
Weight at entry (kg)				
<55	44	66	1.0	Referent
55–59	51	56	1.6	0.9–2.8
60–64	43	48	1.6	0.9–2.9
65–74	70	60	2.2	1.3–3.8
≥75	42	49	2.0	1.1–3.8
No. of previous breast biopsies				
0	192	240	1.0	Referent
1	36	31	1.2	0.7–2.1
≥2	23	12	2.1	1.0–4.6

* Unknowns excluded from analysis.

† Each odds ratio adjusted for parenchymal pattern, age at entry (continuous variable), and other tabulated risk factors.

TABLE 3

Breast cancer odds ratios associated with mammographic parenchymal patterns by first-degree family history of breast cancer, Breast Cancer Detection and Demonstration Project, 1973–1980

Family history of breast cancer	Parenchymal pattern	No. of controls	No. of cases	Odds ratio*	95% confidence interval
No	N1	40	20	1.0	Referent
	P1	79	47	1.2	0.6–2.3
	P2 + DY	124	111	2.2	1.2–4.2
Yes	N1	8	4	0.9	0.2–3.4
	P1	9	17	3.7	1.4–9.9
	P2 + DY	23	52	5.5	2.6–11.8

* Adjusted for age at entry (continuous variable) and weight at entry (<55, 55–59, 60–64, 65–74, and ≥75 kg).

breast cancer (OR = 0.9) compared with N1 women with no such family history. Some caution in the interpretation of this finding is necessary because of the small number of women in the N1 category who had a family history of breast cancer. Although our test for multiplicative interaction was not statistically significant ($p = 0.30$), we observed a significant interaction based on the additive model ($p < 0.05$).

When stratified by age at entry into the Breast Cancer Detection and Demonstration Project (table 4), women aged 46–60 years had higher breast cancer odds ratios associated with the P1 (OR = 2.9) and P2 + DY (OR = 5.8) patterns than did women in the younger or older age groups. We observed no increased risk of breast cancer associated with the P2 + DY category among women aged 45 years and younger

Breast cancer odds ratio

Age at entry(years)
≤45
46–60
>60

* Odds ratio from m
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TABLE 4

Breast cancer odds ratios associated with mammographic parenchymal patterns by age and entry, Breast Cancer Detection and Demonstration Project, 1973–1980

Age at entry(years)	Parenchymal pattern	No. of cases	No. of controls	Odds ratio*	95% confidence interval
≤45	N1	5	6	1.0	Referent
	P1	12	9	1.6	0.4–7.1
	P2 + DY	35	49	1.0	0.3–3.5
46–60	N1	7	29	1.0	Referent
	P1	39	53	2.9	1.1–7.4
	P2 + DY	91	74	5.8	2.4–13.6
>60	N1	12	13	1.0	Referent
	P1	13	26	0.6	0.2–1.6
	P2 + DY	37	24	2.2	0.8–5.8

* Odds ratio from model including age at entry (≤45, 46–60, and >60 years), weight at entry (<55, 55–59, 60–64, 65–74, and ≥75 kg), parenchymal pattern (N1, P1, and P2 + DY), and parenchymal pattern × age at entry (interaction p value = 0.0164).

(OR = 1.0), whereas women over the age of 60 had an odds ratio of 2.2. The test for interaction between age at entry and parenchymal pattern classification on breast cancer risk indicated an effect in excess of the multiplicative model (p = 0.02). The fact that age was a matching factor in this study precluded examination of the joint effects of age and parenchymal pattern under the additive model (28).

We also examined odds ratios associated with the P2 + DY categories by menopausal status at time of entry into the Project. The estimates of breast cancer risk among women with the P2 + DY patterns were somewhat higher among postmenopausal (OR = 3.4, 95 per cent CI: 1.7–6.7) than among premenopausal (OR = 2.0, 95 per cent CI: 0.7–5.7) women. Some caution in interpreting the odds ratio for premenopausal women is warranted because few of these women had the N1 pattern. There was no evidence of interaction assuming either a multiplicative or an additive model.

To evaluate interobserver reliability, one of the authors (J. N. W.) blindly reclassified 291 caudal-lateral mammogram pairs according to parenchymal pattern category (table 5). Agreement between the two readings on the four pattern categories was 74.6 per cent. When the P2 and DY categories were combined, the overall agreement rose to 82.1 per cent. In addition, intraobserver reliability improved with image quality, as judged by one of the authors (J. N. W.) at the time of each assessment.

TABLE 5

*Cross-tabulation of first and second readings of reliability sample mammograms, Breast Cancer Detection and Demonstration Project, 1973–1980**

Second reading	First reading				
	N1	P1	P2	DY	Total
N1	43	10	0	0	53
P1	12	70	10	6	98
P2	1	9	76	13	99
DY	2	2	9	28	41
Total	58	91	95	47	291

* Per cent agreement between the first and second reading (N1, P1, P2, and DY) = 74.6%. Per cent agreement when the P2 and DY categories were combined (N1, P1, and P2 + DY) = 82.1%.

DISCUSSION

This study provides additional evidence that mammographic parenchymal patterns are indicators of risk for the subsequent development of breast cancer, independent of recognized breast cancer risk factors. Of particular importance was the finding that the increased breast cancer risk associated

with the P2 + DY pattern category was apparent using mammograms taken four years before breast cancer diagnosis. In addition, this is the only study in which Dr.Wolfe, as sole classifier, read all of the mammograms without knowledge of the disease status.

Of the risk factors considered as confounders, only weight at entry had an appreciable effect on the odds ratios associated with mammographic patterns. Other investigators have also observed that weight can confound such analyses (34, 35). Because controlling for age and weight tends to increase odds ratio estimates associated with the pattern categories, studies that did not adjust for these variables may have underestimated the strength of the association of parenchymal patterns with breast cancer risk (23).

Although estimates of breast cancer risk associated with mammographic patterns have varied widely across studies, our finding of a significantly increased risk of breast cancer associated with the P2 and DY parenchymal patterns agrees with findings from several other case-control (7, 8, 14, 15, 18, 34) and prospective (5, 9, 10, 12) studies. Our finding of similar odds ratios associated with the P2 and DY patterns is consistent with those reported from several well-conducted studies (14, 20, 34). Our findings agree closely with those of Carlile et al. (20), the only other case-control study of which we are aware that used prediagnostic mammograms in classifying mammographic patterns. In addition, these investigators worked closely with Dr. Wolfe in order to replicate his classification with reasonable interobserver agreement (36).

Our most striking finding was the increased risk of breast cancer seen among women who had both a first-degree family history of breast cancer and the P2 or DY parenchymal pattern compared with women in the N1 category who did not have such a family history. Furthermore, a positive family history was not a risk factor among women whose parenchymal pattern was classified as N1. Although the interaction between parenchymal pattern and family history of breast cancer was statistically significant only under the additive model, suggesting that the joint effect of these two variables exceeded the sum of their individual effects, it is reassuring that the observed odds ratio also exceeded that expected under the multiplicative model. Thus, whether rate differences or rate ratios were used as the measure of effect, our conclusions remained the same.

Although the relation of parenchymal patterns to atypical hyperplasia has not been established, it is noteworthy that Dupont and Page (37) found a similar interaction of family history of breast cancer with atypical hyperplasia. These investigators found that women with a first-degree family history of breast cancer had high relative risks of the disease associated with atypical hyperplasia. In line with these findings, Brinton et al. (38) found evidence of a synergistic relation between the presence of a first-degree family history of breast cancer and a history of multiple biopsies for benign breast disease among cases and controls from the Breast Cancer Detection and Demonstration Project.

In our study, the relative risk of breast cancer associated with mammographic patterns appeared to be modified by age. We observed the highest odds ratios associated with the P2 + DY patterns among women aged 46–60 years. In contrast, we found no increased risk associated with P2 + DY among women aged 45 years and younger, whereas women over age 60 had an odds ratio of 2.2. We find it difficult to explain this up-and-down trend in odds ratios with age and cannot rule out the possibility that the finding of a significant interaction occurred by chance. In the same study population, Carlile et al. (20) and Whitehead et al. (35) also found an interaction of parenchymal patterns with age in which a high risk of breast cancer was associated with the P2 and DY patterns among women aged 55–59 years, but considered the interaction a spurious finding. Results from several other studies that evaluated the association

of mammographic patterns with breast cancer within separate age groups have varied considerably (21). Whereas some studies found no differences in the breast cancer risk associated with parenchymal patterns by age (34, 39), others reported positive associations with the P2 or DY pattern only among women under ages 50–60 years (6, 7, 12, 14) or found the strongest association among women aged 50–60 years and older (9, 21).

Several features of the design of this investigation should have minimized the opportunity for bias to influence our findings. Mammograms of the ipsilateral breast four years before diagnosis were read in a blinded manner, making it unlikely that Dr. Wolfe was biased by the presence of tumors on the study mammograms. Moreover, the reliability data indicated that intraobserver consistency was good, showing 82.1 per cent agreement. In addition, information on potentially confounding variables was obtained and controlled for in the analysis. The fact that all cases were diagnosed during the fifth year of the Project might distinguish them from cases detected in previous years, since these women had to be motivated to remain in the Project; however, this potential bias was minimized by matching the cases to controls who also attended the fifth screening examination. Finally, the probability of bias due to the "masking hypothesis," whereby breast tumors are more readily detected in the radiolucent N1 and P1 breasts, should be considered (35, 40). Because masking is believed to influence estimates of relative risk only in studies of prevalent cases and of populations not regularly screened by mammography (35), the effect of masking bias in our study of screened incident cases is likely to be minor.

In conclusion, our findings indicate that mammographic parenchymal patterns serve as indicators of breast cancer risk that are independent of the accepted risk factors for breast cancer. The breast cancer risk associated with the P2 + DY category appears to be highest among women with a first-degree family history of breast cancer. In addition, women between the ages 46 and 60 years who have the P2 or DY pattern may be at higher risk of breast cancer than P2 and DY women of other ages. Use of the mammographic classification to identify such high-risk groups will enable clinicians to more accurately distinguish between categories of women in need of close surveillance for the early detection of breast cancer.

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